

# Comparison of transvaginal ultrasonography, office hysteroscopy, and operative hysteroscopy results in patients with detected endometrial pathology

Comparison of ultrasonography and hysteroscopy for endometrial pathology

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## Abstract

**Aim:** This study aims to compare the diagnostic accuracy of transvaginal ultrasonography (TVUSG), office hysteroscopy (HSK), and operative hysteroscopy (HSK) in patients with endometrial pathology and to evaluate their superiority in terms of effectiveness and reliability.

**Materials and Methods:** The data of 912 female patients who were referred to the gynecology outpatient clinic of the Department of Obstetrics and Gynecology between January 2012 and July 2019 and who were diagnosed with endometrial pathology during examination were retrospectively reviewed. The patients included in the study underwent pelvic examination, transvaginal ultrasonography, and diagnostic hysteroscopy, respectively, and the pathological results were compared with the preliminary diagnoses.

**Results:** The mean age was 44.72±9.77. Ultrasonography revealed 60% polyps, 10.7% fibroids, 12.7% normal findings, and 16.6% other pathologies. Office HSK detected 53.7% polyps, 5.3% fibroids, 29.6% normal findings, and 11.2% other pathologies; operative HSK detected 71% polyps, 12.4% fibroids, 8.2% normal findings, and 7.4% other pathologies. The overall sensitivity of TVUSG was 91.2%, specificity 23.4%; the sensitivity of office HSK was 74.2%, specificity 38.5%; the sensitivity of operative HSK was 95.1%, specificity 29.6%.

**Discussion:** Transvaginal ultrasonography, hysteroscopy, and operative hysteroscopy have high accuracy rates in detecting endometrial pathologies. Operative hysteroscopy has the highest diagnostic value in detecting endometrial pathologies. However, all three methods have different advantages and are recommended

to be used in conjunction with each other in patient treatment planning.

## Keywords

endometrial pathology, transvaginal ultrasonography, office hysteroscopy, operative hysteroscopy, fibroid, polyp, hyperplasia

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This study was approved by the Ethics Committee of Taksim Training and Research Hospital (Date: 2019-01-30, No: 18)

## Introduction

Endometrial biopsy is one of the fundamental diagnostic methods frequently used in gynecology for the diagnosis and management of conditions such as abnormal uterine bleeding, endometrial hyperplasia, and endometrial polyps. This method allows for pathological examination by obtaining tissue samples from the uterine cavity and plays a critical role in the clinical decision-making process [1].

Abnormal uterine bleeding is usually a sign of reproductive system pathologies, but it can rarely be an indicator of disorders in other systems [2]. Clinically, this condition can be associated with polyps and fibroids in 20% of cases during adolescence; it has been associated with pathologies such as polyps, fibroids, hyperplasia, or endometrial cancer in 30% of cases during the reproductive period and in 50% of cases during the perimenopausal period [3,4].

In recent years, with the advancement of imaging technologies, different methods have become widespread in the evaluation of endometrial pathologies. These methods include transvaginal ultrasonography (TVUSG), hysterosalpingography (HSG), saline infusion sonography (SIS), hysteroscopy (HSK), and magnetic resonance imaging (MRI). Transvaginal ultrasonography, in particular, stands out as a fast and non-invasive method with a high accuracy rate in the evaluation of uterine pathologies [5]. HSK has become an important option for both diagnosis and treatment due to its minimally invasive nature and applicability in outpatient settings [6].

This study aims to compare the diagnostic accuracy of TVUSG, Office HSK, and operative HSK in patients with endometrial pathology and to evaluate the superiority of these methods in terms of effectiveness and reliability.

## Materials and Methods

January 2012-July 2019, the data of 1,998 female patients who visited the gynecology outpatient clinic of the Department of Obstetrics and Gynecology at a tertiary education and research hospital, were diagnosed with endometrial pathology during examination, and underwent office and/or operative hysteroscopy procedures, were retrospectively reviewed and recorded from the hospital's digital record system and patient files. Due to the lack of standard documentation in some patient files, 912 patients who met the appropriate criteria were included in the study.

Patients of all age groups with endometrial pathology were included in the study. Patients who were pregnant, had bleeding due to imminent or incipient abortion, suspected ectopic pregnancy, or abnormal uterine bleeding due to bleeding diathesis disorder were excluded.

These patients underwent pelvic examination, TVUSG, and office HSK (diagnostic) performed sequentially by the same gynecologist. Operative HSK was performed on patients based on the pathologies observed during office HSK.

TVUSG (DC-7, Mindray, Shenzhen, China) was performed at the time of the patient's initial visit to the outpatient clinic, regardless of the patient's menstrual phase. The probe was inserted into the vagina, and the cervix, cervical canal, endometrial cavity contours, and ovaries were evaluated using

coronal and sagittal sections.

In this study, the uterine cavity and endometrium were evaluated as normal endometrium when they were clearly separated from the myometrium and appeared as a hyperechoic and regular line. All structures with different echogenicity and structures that disrupted the continuity of the uterine cavity and caused an irregular appearance were considered abnormal. Endometrial polyps were evaluated as hyperechoic masses with regular borders, varying in size and shape. Structures within the uterine cavity that were less echogenic than polyps and had a dense structure were evaluated as uterine myomas. Abnormalities such as myomas and polyps found in the cavity were recorded. Endometrial thickness was measured in the sagittal plane from the outer border of the endometrium at its thickest point to the outer border of the underlying endometrium. Patients with endometrial thickness above 5 mm in the postmenopausal period were evaluated as having increased endometrial thickness. Fluid in the endometrial cavity was not included in the measurement.

The hysteroscopy device used in office HSK was Olympus (Olympus, Tokyo, Japan), and the hysteroscope used in conventional hysteroscopy was MED-15 (Medikal Co., İstanbul, Turkey). The Office HSK procedure was performed under the supervision of an obstetrician-gynecologist with sufficient knowledge and skills, assisted by an intervention nurse with sufficient knowledge and experience regarding the device. The patients' questions were answered. The consent form was signed.

Cases scheduled for office HSK were placed on the examination table in the lithotomy position. Prophylactic antibiotics were not used. The cervical canal was evaluated while passing through the cervical os. After entering the cavity, each tubal ostium and the walls of the uterine cavity were evaluated in detail using panoramic imaging. Pathologies detected during the procedure and their locations were noted in the system. Preparations for operative HSK were initiated in patients with detected pathologies. In patients with no pathology detected during office HSK but with symptoms such as abnormal uterine bleeding or postmenopausal bleeding, endometrial sampling was performed.

In operative HSK, endometrial polyps, submucosal myomas, intrauterine adhesions, and uterine septa that could be treated during the procedure were removed with the aid of a resectoscope. Endometrial sampling was performed in patients without any pathology. All samples taken were sent to the hospital's pathology department.

## Statistical Analysis

IBM SPSS Statistics 22 (IBM SPSS, Turkey) software was used for statistical analysis when evaluating the findings obtained in the study. The normality of the parameters was assessed using the Shapiro-Wilk test when evaluating the study data. In addition to descriptive statistical methods (mean, standard deviation, frequency), the Chi-square test and Fisher-Freeman-Halton test were used to compare qualitative data when evaluating the study data. Diagnostic screening tests were used in sensitivity and specificity calculations. Significance was evaluated at  $p < 0.05$ .

Ethical Approval

This study was approved by the Ethics Committee of Taksim Training and Research Hospital (Date: 2019-01-30, No: 18).

Results

The ages of the women ranged from 20 to 82, with an average of 44.72±9.77. The demographic data of the patients are given in Table 1. Of the 47 women whose smoking status was known, 95.7% were smokers and 4.3% were non-smokers. We classified patients' presenting complaints as premenopausal, postmenopausal, amenorrhea-oligomenorrhea, and other. We included patients describing menometrorrhagia, menorrhagia,

metrorrhagia, hypermenorrhea, and hypomenorrhea in the premenopausal group; patients describing bleeding during the postmenopausal period or those with detected postmenopausal endometrial thickening in the postmenopausal group; and patients describing pelvic pain, infertility, postcoital bleeding, dysmenorrhea, vaginitis, and dyspareunia complaints in the group we called "other."

The pathological results according to the groups of presenting complaints are presented in Table 1. There was a statistically significant difference in the distribution rates of pathology results among the complaint groups (p = 0.000; p < 0.05). The rate of polyps in the pathology results of the group presenting

Table 1. Demographic characteristics and pathology results were evaluated according to presenting complaints

|                                                                      |                        | Min-Max                  | Mean±SD                                  |                 |
|----------------------------------------------------------------------|------------------------|--------------------------|------------------------------------------|-----------------|
| Age(n=912)                                                           |                        | 20-82                    | 44.72 ± 9.77                             |                 |
| Parity (n=634) (medyan)                                              |                        | 0-10                     | 2.68 ± 1.83(2)                           |                 |
| Mode of delivery (n=572)                                             |                        | n                        | %                                        |                 |
| None                                                                 |                        | 7                        | 1.22                                     |                 |
| NSD                                                                  |                        | 345                      | 60.32                                    |                 |
| C/S                                                                  |                        | 118                      | 20.63                                    |                 |
| NSD+C/S                                                              |                        | 102                      | 17.83                                    |                 |
| Complaint of application                                             |                        |                          | p                                        |                 |
| Pathology result                                                     | Premenopausal<br>n (%) | Post menopausal<br>n (%) | Amenorrhoea-<br>Oligomenorrhoea<br>n (%) | Others<br>n (%) |
| Polyps                                                               | 393 (%63.5)            | 20 (%46.51)              | 21 (%48.8)                               | 135 (%65.2)     |
| Fibroid                                                              | 62 (%10)               | 1 (%2.33)                | 4 (%9.3)                                 | 9 (%4.3)        |
| Malignancy                                                           | 8 (%1.3)               | 5 (%11.63)               | 2 (%4.7)                                 | 2 (%1)          |
| Normal                                                               | 151 (%24.4)            | 17 (%39.53)              | 15 (%34.9)                               | 61 (%29.5)      |
| Polyp+Fibroid                                                        | 5 (%0.8)               | 0 (%0)                   | 1 (%2.3)                                 | 0 (%0)          |
| 1Ki-kare test *p<0.05. NSD=Normal Spontaneous Delivery CS: C-section |                        |                          |                                          |                 |

Table 2. Distribution of pathology results according to the results of diagnostic methods

| Pathology result | Ultrasonography |               |              |             |                     |             |
|------------------|-----------------|---------------|--------------|-------------|---------------------|-------------|
|                  | Polyp n (%)     | Fibroid n (%) | Normal n (%) | Other n (%) | Total n (%)         |             |
| Polyp            | 450 (%82.3)     | 18 (%18.4)    | 56 (%48.3)   | 45 (%29.8)  | 569 (%62.4)         |             |
| Fibroid          | 6 (%1.1)        | 66 (%67.3)    | 3 (%2.6)     | 1 (%0.7)    | 76 (%8.3)           |             |
| Malignancy       | 10 (%1.8)       | 1 (%1)        | 0 (%0)       | 6 (%4)      | 17 (%1.9)           |             |
| Normal           | 78 (%14.3)      | 10 (%10.2)    | 57 (%49.1)   | 99 (%65.5)  | 244 (%26.7)         |             |
| Polyp+Fibroid    | 3 (%0.5)        | 3 (%3.1)      | 0 (%0)       | 0 (%0)      | 6 (%0.7)            |             |
| Office HSK       |                 |               |              |             |                     |             |
| Pathology result | Polyp n (%)     | Fibroid n (%) | Normal n (%) | Other n (%) | Polyp+Fibroid n (%) | Total n (%) |
| Polyp            | 284 (%72.3)     | 8 (%20.5)     | 118 (%54.4)  | 29 (%35.4)  | 0 (%0)              | 439 (%60)   |
| Fibroid          | 14 (%3.6)       | 26 (%66.7)    | 12 (%5.5)    | 1 (%1.2)    | 0 (%0)              | 53 (%7.2)   |
| Malignancy       | 10 (%2.5)       | 1 (%2.6)      | 2 (%0.9)     | 1 (%1.2)    | 0 (%0)              | 14 (%1.9)   |
| Normal           | 81 (%20.6)      | 4 (%10.2)     | 85 (%39.2)   | 51 (%62.2)  | 0 (%0)              | 221 (%30.2) |
| Polyp+Fibroid    | 4 (%1)          | 0 (%0)        | 0 (%0)       | 0 (%0)      | 1 (%100)            | 5 (%0.7)    |
| Operative HSK    |                 |               |              |             |                     |             |
| Pathology result | Polyp n (%)     | Fibroid n (%) | Normal n (%) | Other n (%) | Polyp+Fibroid n (%) | Total n (%) |
| Polyp            | 256 (%89.20)    | 8 (%16)       | 16 (%48.5)   | 15 (%50)    | 3 (%75)             | 298 (%73.8) |
| Fibroid          | 5 (%1.74)       | 35 (%70)      | 1 (%3)       | 0 (%0)      | 0 (%0)              | 41 (%10.1)  |
| Malignancy       | 5 (%1.74)       | 1 (%2)        | 0 (%0)       | 1 (%3.3)    | 0 (%0)              | 7 (%1.7)    |
| Normal           | 19 (%6.62)      | 5 (%10)       | 16 (%48.5)   | 14 (%46.7)  | 0 (%0)              | 54 (%13.4)  |
| Polyp+Fibroid    | 2 (%0.70)       | 1 (%2)        | 0 (%0)       | 0 (%0)      | 1 (%25)             | 4 (%1)      |
| HSK=Hysteroscopy |                 |               |              |             |                     |             |

**Table 3.** Distribution of pathology detection rates according to diagnostic methods

| Pathology       |                   |                 |                |
|-----------------|-------------------|-----------------|----------------|
|                 | Abnormal<br>n (%) | Normal<br>n (%) | Total<br>n (%) |
| Ultrasonography |                   |                 |                |
| Abnormal        | 609 (%66.8)       | 187 (%20.5)     | 796 (%87.3)    |
| Normal          | 59 (%6.5)         | 57 (%6.3)       | 116 (%12.8)    |
| Total           | 668 (%73.2)       | 244 (%26.8)     | 912 (%100)     |
| Office HSK      |                   |                 |                |
| Abnormal        | 379 (%51.8)       | 136 (%18.6)     | 515 (%70.4)    |
| Normal          | 132 (%18)         | 85 (%11.6)      | 217 (%29.6)    |
| Total           | 511 (%69.8)       | 221 (%30.2)     | 732 (%100)     |
| Operative HSK   |                   |                 |                |
| Abnormal        | 333 (%82.4)       | 38 (%9.4)       | 371 (%91.8)    |
| Normal          | 17 (%4.2)         | 16 (%4)         | 33 (%8.2)      |
| Total           | 350 (%86.6)       | 54 (%13.4)      | 404 (%100)     |

HSK: Hysteroscopy

with other complaints (65.2%) was found to be statistically significantly higher than that of the postmenopausal (46.51%) and amenorrhea-oligomenorrhea (48.8%) groups ( $p_1 = 0.002$ ;  $p_2 = 0.022$ ;  $p < 0.05$ ). The rate of polyps in the pathology results of the group presenting with premenopausal complaints (63.5%) was statistically significantly higher than that of the postmenopausal group (46.51%); however, the rate of malignancy (1.3%) was significantly lower than that of the postmenopausal group (11.63%) ( $p = 0.000$ ;  $p < 0.05$ ). There was no statistically significant difference in pathology results among the other complaint groups ( $p > 0.05$ ).

The distribution of pathology results according to diagnostic methods is shown in Table 2. Pathology results confirmed polyps in 82.3% of cases, with ultrasound results indicating polyps. Pathology results confirmed fibroids in 67.3% of cases, with ultrasound results indicating fibroids. Of the cases with normal ultrasound results, 48.3% were diagnosed as polyps, and 49.1% were diagnosed as normal by pathology. Of the cases with other ultrasound results, 65.5% were diagnosed as normal by pathology. Of the cases with polyps according to office HSK results, 72.3% were also diagnosed as polyps according to pathology. Of the cases with fibroid on office HSK, 66.7% were also diagnosed as fibroid on pathology. Of the cases with normal findings on office HSK, 54.4% were diagnosed as polyps on pathology, and 39.2% were diagnosed as normal. Of the cases with other findings on office HSK, 62.2% were diagnosed as normal on pathology. Of the cases with polyps on operative HSK, 89.2% were also diagnosed as polyps on pathology. Of the cases with fibroids on operative HSK, 70% were also diagnosed as fibroids on pathology. Of the cases with normal operative HSK results, 48.5% were diagnosed as polyps on pathology, and 48.5% were diagnosed as normal. Of the cases with other findings on operative HSK, 50% were diagnosed as polyps on pathology, and 46.7% were found to be normal. Of the cases with polyp+fibroid on operative HSK, 75% were diagnosed as polyps on pathology.

The distribution of diagnostic methods for identifying pathology is shown in Table 3. Of the 668 cases with an abnormal pathology diagnosis, 609 (66.8%) were detected as

abnormal on ultrasound. The sensitivity of ultrasound relative to pathology was 91.2%, specificity was 23.4%, positive predictive value (PPV) was 76.5%, and negative predictive value (NPV) was 49.1%. Of the 511 cases with an abnormal pathology diagnosis, 379 (51.8%) were detected as abnormal by office HSK. The sensitivity of office HSK compared to pathology was 74.2%, specificity was 38.5%, PPV was 73.6%, and NPV was 39.2%. Of the 350 cases diagnosed as abnormal by pathology, 333 (82.4%) were detected as abnormal by operative HSK. The sensitivity of operative HSK relative to pathology was 95.1%, specificity was 29.6%, PPV was 89.8%, and NPV was 48.5%.

Discussion

In this study, the success rates of methods used in the diagnosis of endometrial pathologies were evaluated, and operative hysteroscopy was determined to be the most effective method. Visual examination-based diagnostic methods were found to have lower accuracy rates compared to ultrasonography, and ultrasonography was found to perform better than office hysteroscopy. These findings suggest that the physician's experience and expertise may play a critical role in the effectiveness of imaging methods [7].

In this study, polyps were the most frequently detected finding in both intraoperative hysteroscopic observation and histopathological examination. Similarly, in the study by Altınbaş et al., polyps were the most frequently detected finding in intraoperative hysteroscopic observations, while histopathological examinations largely resulted in endometrial polyp diagnoses [8]. Although the results of the study are largely consistent with the literature, it should be noted that they may vary depending on the characteristics of the patient population. The high polyp rate found in the study is thought to be due to the large number of patients and the fact that our sample consisted largely of patients in the reproductive and premenopausal periods. Furthermore, the evaluation of endometrial differences within the 'normal' group may have led to a relatively high normal rate in the pathology results. The small number of postmenopausal patients may explain the low malignancy rate.

In the study by Çepni et al., it was found that TVUSG and sonohysterography (SIS) had limited sensitivity in the diagnosis of endometrial polyps in the postmenopausal period, whereas diagnostic accuracy was significantly increased with hysteroscopy [9]. In a retrospective analysis by Cengiz et al., it was reported that the most frequently detected pathology in cases undergoing operative hysteroscopy was endometrial polyps, while myomas were seen at lower rates [10]. The findings of the obtained study are largely consistent with the literature.

Alborzi et al. reported that the diagnostic accuracy of TVUSG was limited, whereas SIS provided higher sensitivity and specificity [11]. Similarly, Yıldırım et al.' study also revealed that TVUSG showed moderate performance in identifying intracavitary lesions [12]. Furthermore, it was determined that abnormal cases detected by TVUSG showed high sensitivity but low specificity.

The effectiveness of HSK in the diagnosis of endometrial pathologies is well known. In this study, office HSK yielded

acceptable results in terms of sensitivity and positive predictive value, but specificity and negative predictive value were lower. The literature indicates that the sensitivity rates of hysteroscopy are generally reported to be high [13-15]. The results of operative HSK were found to have a very high sensitivity, consistent with the literature, while similarly limited values were obtained in terms of specificity [16]. In a study investigating the diagnostic accuracy of HSK in perimenopausal and postmenopausal women, high sensitivity was reported for benign endometrial pathologies [17]. In a prospective study conducted by Al-Asadi on 60 women, the diagnostic performance of HSK varied; sensitivity was 100% for polyps, 83% for fibroids, and 84.2% for endometrial hyperplasia, while sensitivity for endometrial cancer was reported to be only 50%. The study also emphasized that specificity values were low. These findings show that the low specificity rates in our series are also observed in the literature and that HSK may be limited, especially in the diagnosis of malignancy. Therefore, it is once again emphasized that HSK findings must be supported by histopathological examination [18].

The low specificity of operative HSK is primarily due to physiological changes in the endometrium, benign polypoid structures, or subendometrial bleeding foci being mistakenly interpreted as pathological lesions, which increases false positive rates. Operator inexperience, lack of confirmatory second operator evaluation, inadequate viewing angle, or technical problems can also negatively affect diagnostic accuracy. Furthermore, heterogeneous lesions or small superficial foci may appear pathological during hysteroscopy but may not yield meaningful findings on histopathological examination. In addition, diagnostic discrepancies due to heterogeneity may arise in pathology sampling, which is considered the gold standard, leading to inconsistent results with hysteroscopy. Particularly in postmenopausal cases, findings such as endometrial atrophy and irregular bleeding can easily be confused with pathological processes, contributing to low specificity.

However, there are studies in the literature reporting higher diagnostic efficacy of HSK with biopsy. Indeed, in a large-scale retrospective cohort analysis conducted by Öztürk et al. on 2054 premenopausal women, biopsy performed with HSK provided the highest diagnostic accuracy, and specificity values were also reported as the highest among all methods [19]. In a retrospective analysis conducted by Khalife et al. on a large patient series, the diagnostic performance of endometrial sampling guided by hysteroscopy was evaluated, and high sensitivity and specificity values were found [20]. This difference may be due to the retrospective design, operator experience, and differences in the criteria used for evaluation. Therefore, it is thought that the hysteroscopy-guided biopsy method may make an important contribution, particularly in increasing specificity, and should be preferred in future studies. Of study this

A study by Garutti et al. on postmenopausal cases reported that HSK has a very high sensitivity and specificity [21]. In this study, office HSK also showed high sensitivity in the postmenopausal group, but a significant limitation was observed in terms

of specificity. TVUSG showed moderate performance in the diagnosis of endometrial polyps, while office HSK fell below the reported values in the literature [22,23]. This difference can largely be attributed to operator inexperience.

In the diagnosis of submucosal fibroids, the literature indicates that office HSK offers a wide range of sensitivity [18-23]. In this study, operative HSK demonstrated high sensitivity and specificity in detecting fibroids, while office HSK showed lower sensitivity. This situation may be due to the inability to fully evaluate fibroids with office HSK or their confusion with polyps. When the need for additional treatment was evaluated in patients who underwent hysteroscopy, it was determined that 91.2% of 875 cases did not require additional treatment. The need for additional treatment after hysteroscopic polypectomy has been reported to be between 8-10% in the literature [24]. In this study, the complication rate after the procedure was determined to be 1.4%. The complication rate was reported as 3.3% in the study by Cengiz et al. and 3% in the study by Karakaş et al. [10,25]. These results show that the complication rate in our study is lower than that reported in the literature.

#### **Limitatitons**

The retrospective design of our study constitutes a significant methodological limitation. Retrospective design increases the risk of selection bias in patient selection and may lead to information bias depending on how the data is recorded. This situation may negatively affect diagnostic accuracy and reliability, particularly during retrospective evaluation of clinical findings and imaging results. Furthermore, the low specificity values obtained in our study led to more frequent false-positive results and limited the direct generalizability of the findings to clinical practice. Office HSK results may have been affected by the operator's learning curve and the difficulties encountered, particularly in distinguishing between polyps and submucosal fibroids. This may explain why office hysteroscopy in this study had lower sensitivity compared to the literature. A significant limitation of this study is the relatively small number of postmenopausal cases. This has reduced the ability to detect malignancy and limited the generalizability of the results. Further studies involving larger patient populations, particularly with a higher representation of postmenopausal women, are needed.

Although this study had a large number of patients, was performed by a single operator, and compared different techniques, it was not evaluated in conjunction with a cost analysis. Multicenter studies conducted with cost analyses could contribute to the literature.

#### **Conclusion**

Operative HSK has been shown to be the method with the highest success rate in the diagnosis of endometrial pathologies. Due to the low sensitivity of HSK in endometrial hyperplasia, the necessity of obtaining a biopsy, especially in suspicious cases, should be emphasized. All three methods have different advantages and are recommended to be used together in patient treatment planning.

#### **Scientific Responsibility Statement**

*The authors declare that they are responsible for the article's scientific content, including study design, data collection, analysis and interpretation, writing,*



and some of the main line, or all of the preparation and scientific review of the contents, and approval of the final version of the article.

**Animal and Human Rights Statement**

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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**Conflict of Interest**

The authors declare that there is no conflict of interest.

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